REMARKS

Claims 1-9 are pending. Claims 1-8 have been withdrawn from further consideration as being drawn to non-elected inventions. Claim 9 has been amended to better clarify what Applicants regard as the invention. Support for the amendment can be found in the specification on page 2, lines 31-34 continuing on to page 3, lines 1-5. Further support can be found on page 10, lines 23-25 and on page 10, lines 27-31 continuing on to page 11, line 1. Further support can be found on page 11, lines 9-15, page 12, lines 12-21, and page 13, lines 8-21. No new matter has been introduced by way of this amendment. Thus, claim 9 remains under consideration. Reconsideration of this application is respectfully requested.

Also included herein is a Petition to Correct Inventorship, executed statements by the Assignee and the new inventor, as well as a copy of the Oath and Declaration from the parent application and a fee to cover the Petition to Correct Inventorship.

A Replacement Sheet with correctly labeled Figure 7 is also included.

Petition to Correct Inventorship

The Examiner has noted that a copy of a previously submitted petition filed in the parent application to correct inventorship under 37 CFR 1.324 was denied entry into the present continuation application.

Applicants include herewith a new petition under 37 CFR 1.48, with executed statements from the assignee and the new inventor, along with a copy of the signed oath and declaration from the parent application and the fee to cover the petition for correction of inventorship.

Applicants respectfully request that the petition be granted and that the present application be amended to name the correct inventors.

Objections to Figures

The Examiner has objected to Figure 7 since it is incorrectly labeled. Applicants submit herewith a properly labeled Replacement Sheet for Figure 7. Withdrawal of the objection is respectfully requested.

Claim Rejections under 35 USC §112

The Examiner has rejected claim 9 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to predictably use the invention as claimed. Furthermore, the Examiner has rejected claim 9 under 35 U.S.C. §112, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the invention.

Applicants respectfully traverse the Examiner's rejection and have amended the claim to better describe what Applicants regard as the invention.

Applicants previously provided a declaration under 37 CFR 1.132 which attested to protocols and compilation of data obtained from a series of experiments performed in the laboratory of the inventor. As noted in the previous response, those experiments were provided as confirmatory evidence that an inhibitor of Gli1 could function as an antagonist of its activity and inhibit proliferation of tumor cells.

The Examiner alleges that the data supplied with the declaration is not commensurate in scope with the specification and claims as originally filed. Applicants respectfully traverse the Examiner's rejection and interpretation of the data provided in the declaration.

Applicants direct the Examiner's attention to the specification on page 2, lines 31-34 continuing on to page 3, lines 1-5:

> "Still further, the invention includes the development of therapeutic **agents that are capable of controlling the expression and/or activity/function and expression of *Gli1*, and are thereby able to inhibit the development and/or treat sporadic basal cell carcinoma in animals, and particularly in humans.** Such agents may include **small molecules, ligands, and other agents that would function as *Gli1* antagonists or would otherwise interrupt *Gli1* expression and activity**. Suitable pharmaceutical compositions could be administered by a variety of routes, including topical, oral, parenteral, intrathecal, intranasal, and the like, at a dosage level and schedule that may be determined by the clinician in accordance with the particular condition of the patient."

Furthermore, on page 10, lines 23-25:

> "Thus, in instances where it is desired to reduce or inhibit the activity resulting Gli1 presence and expression, an appropriate inhibitor of such activity, or of Gli1 could be introduced to block the interaction of those factors causally connected therewith."

Yet further on page 10, lines 27-31 to page 11, line 1:

> "As discussed earlier, Gli1 or its binding partners or other ligands or **agents exhibiting either mimicry or antagonism to it or control over its production, may be prepared in pharmaceutical compositions**, with a suitable carrier and at a strength effective for administration by various means to a patient experiencing an adverse medical condition associated with Gli1 activity or expression specific for the treatment thereof."

The Applicants have provided evidence as to the role of Gli1 expression in basal cell carcinoma. For example, in Example 1, Applicants have shown that ectopic expression of Gli1 in tadpole epidermis results in tumor formation. In addition, Example 2 demonstrates that if one injects Gli 1 RNA into frog embryos, the epidermal cells which inherit the injected Gli 1 RNA, as shown by lineage tracing analysis, display atypical morphology. Furthermore, external analysis of the tadpoles shows prominent tumors of the skin. Taking this one step further, the Applicants also addressed the possibility that Gli 1 activation and ectopic expression of Gli 1 could play a role in the development of adult sporadic BCC, and assayed spontaneously occurring human BCC's for Gli1 expression. In situ hybridization studies showed that elevated levels of Gli1 expression were observed in all but one sample tested, thus strengthening the Applicant's position as to a relationship between Gli 1 expression and its role in tumorigenesis.

Accordingly, because there was a strong correlation between the cellular dysplasia, tumor formation and the presence of Gli 1 in the tumor cells, it was likely that agents that inhibit the expression and/or function of Gli 1 were probable candidates as inhibitors of cellular proliferation and tumor growth and would be effective when delivered to a subject in need of such therapy by way of a pharmaceutical composition.

The data to support the effect of an antagonist to Gli 1 (as claimed) on tumor cell growth was provided in the declaration under 37 CFR 1.132. While the specification does not directly disclose the siRNA molecules provided as support by the inventor, it is obvious from the data provided that the siRNA molecules act

to inhibit tumor cell proliferation using two different tumor cell systems, U87 and glioblastoma cells. In addition, Applicants have amended claim 9 to include anti-sense molecules and antibodies as antagonists of Gli 1, and have provided additional positive data to support the inclusion of these agents into the pharmaceutical composition claim as currently pending. This data may be found in an article published by the inventor in the journal Development Vol. 128, pages 5201-5212 and is attached herein as Appendix A. More specifically, the anti-tumor activity displayed by the antisense RNA molecules may be found specifically on page 5208 in the paragraph entitled "Activation of endogenous Gli1 function is required for hyperprolliferation".

The Examiner alleges that siRNA molecules were not widely known at the time of filing of the present application, thus, one of skill in the art would not be enabled to practice the invention as claimed. Applicants respectfully point out to the Examiner that siRNA molecules were not previously claimed, and are not presently claimed. However, Applicants have now amended the claim to read on antisense RNA molecules and anti-Gli1 antibodies and have provided support in the specification for such amendments, as well as additional data from the inventor in support of the claim as amended (please see Appendix A). In addition, Applicants have in fact prepared antisense RNA molecules as described in the present application, some of which were used as probes for in situ hybridization. The preparation of such antisense RNA molecules is also described in the paper submitted herein from the inventor as Appendix A (please see page 5203).

Furthermore, the Applicants respectfully request reconsideration of entry of the previously submitted data included with the declaration under 37 CFR 1.132 into the application for the following reason. The Applicants assert that RNA interference occurs through an antisense mechanism of action that utilizes a double stranded RNase to hydrolyze the RNA. Thus, the siRNA molecules may be considered as a subset of anti-sense RNA molecules, which have been fragmented as a result of enzymatic breakdown. The Examiner's attention is drawn to a reference article submitted herein as Appendix B, by Timothy Vickers et al, wherein the authors compared the potency, efficacy, specificity and duration of action of antisense RNAs and siRNAs and found them to be comparable. Accordingly, the data now submitted with antisense RNA molecules as antagonists

of Gli1 and inhibition of tumor cell proliferation corroborate the earlier data submitted with the siRNA molecules as antagonists of Gli1 and inhibitors of tumor cell proliferation. Reconsideration of entry of the earlier filed declaration and data under 37 CFR 1.132 is respectfully requested.

In addition, Applicants provide herewith as Appendix C information related to the use of antisense molecules under study in clinical trials, with the information provided having a publication date of 1994, thus supporting the fact that one of skill in the art could practice the invention as presently claimed at the time of filing of the instant application. Additionally, Appendix D contains copies of U.S. Patent Nos. 5510239 and 5514786 as further support for the antisense concept being known at the time of filing of the present application. This information, combined with the Applicants' own procedures for synthesis of antisense RNA for Gli1 as described in the present application provides support for the enablement and written description of the invention as claimed.

Furthermore, the use of antibody therapy for inhibition of expression and/or function of particular molecules for control of tumor proliferation is widely known in the art. Accordingly, the present application provides support for antibodies to Gli1 and refers to its use as an antagonist of Gli1 expression and/or function. The claims have accordingly been amended to include the antibodies to Gli1 as an antagonist for use in the pharmaceutical composition.

Applicants respectfully request withdrawal of the rejections under 35 USC § 112 for the above reasons.

Fees

A check in the amount of $130 is enclosed to cover the Petition to Correct Inventorship. No other fees are believed to be necessitated by this response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 11-1153 for any underpayment, or to credit any overpayments.

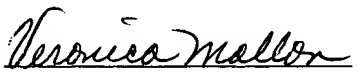
Conclusion

Applicants believe that the outstanding rejections based on 35 U.S.C. §112 have been overcome by the amendments and arguments presented above. Thus, reconsideration and withdrawal of the outstanding grounds of rejection, and early allowance of the claims as amended is believed to be in order and is courteously

solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned at the number listed below, so that prosecution of the application may be expedited.

Respectfully submitted,



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Enclosures: Appendix A, B, C
Petition to Correct Inventorship
Signed Statement by New Inventor
Written Consent of Assignee
Replacement sheet for Figure 7
Copy of Executed Oath and Declaration